PCT / IN 04 / 0 0 3 0 6

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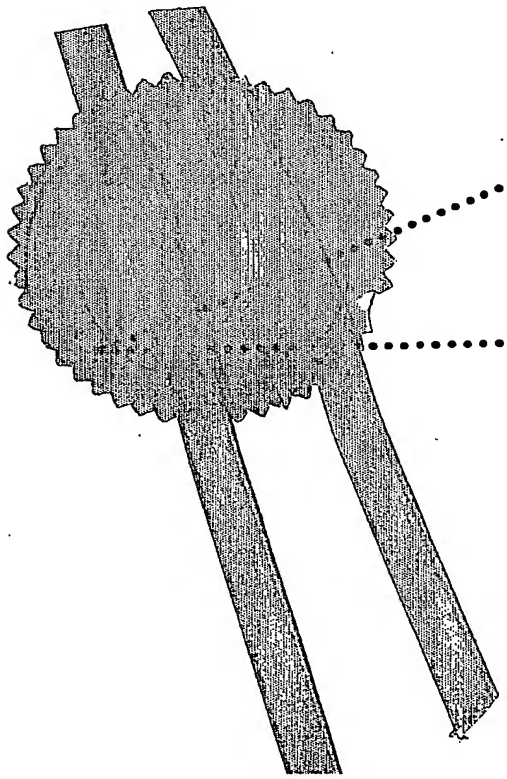
Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Complete Specification filed on 28/04/2003 and post-dated to 01/10/2003 under Section 17(1) of the Patents Act, 1970 in respect of Patent Application No. 417/MUM/2003 of LUPIN LIMITED, 159, CST Road, Kalina, Santacruz (East), Mumbai – 400 098, State of Maharashtra, India, An Indian Company.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act,1970.



Dated this 25th day of Nov 2004.

(R. BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM - 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See sections 5 (2), 7, 54 and 135 and rule 33A]

1. We, a) **LUPIN LIMITED**, b) 159, CST Road, Kalina, Santacruz (East), Mumbai - 400 098, State of Maharashtra, India, c) an Indian company,

2. hereby declare -

   (a) that we are in possession of an invention titled **"A CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION AND A PROCESS FOR PREPARING THE SAME."**

   (b) that the Complete Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

3. further declare that the inventors for the said invention are

a) **SEN Himadri**, b) Lupin Research Park, 46/47A, Nande Village, Taluka Mulshi, Pune – 411 042, State of Maharashtra, India, c) an Indian national.

a) **JAYANTHI Suryakumar**, b) Lupin Research Park, 46/47A, Nande Village, Taluka Mulshi, Pune – 411 042, State of Maharashtra, India, c) an Indian national.

a) **RAGHAVAN Vineeth**, b) Lupin Research Park, 46/47A, Nande Village, Taluka Mulshi, Pune – 411 042, State of Maharashtra, India, c) an Indian national.

a) **ARRA Ganga Srinivas**, b) Lupin Research Park, 46A/47A, Nande Village, Taluka Mulshi, Pune – 411 042, State of Maharashtra, India, c) an Indian national.

417/mum/2003

28/4/2003

Received Rs. 5000/- in Cash
Cheque/D.D./P.O. 28/4/03
Vide Entry ... 30/3 ... the Register of ...

u/s. 17(1) of the Patents Act, 1970.
(Dr. Anuradha Kamat)
Examiner of P & D

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows :

NONE.

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant/patentee:

NOT APPLICABLE.

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on _____ under section 16 of the Act

NOT APPLICABLE.

7. That we are the assignees of the true and first inventors.

8. That our address for service in India is as follows :

S. MAJUMDAR & CO., 5, Harish Mukherjee Road, Calcutta - 700 025, State of West Bengal. Phone : 0-33-24557484/24557485/24557486 ; Fax : 0-33-24557487/24557488.

9. We are the true and first inventors for this invention declare that the applicant(s) herein are our assignee

a) **SEN Himadri**
b) Lupin Research Park, 46/47A, Nande Village, Taluka Mulshi, Pune – 411 042, State of Maharashtra, India
c) an Indian national.

a) **JAYANTHI Suryakumar**
b) Lupin Research Park, 46/47A, Nande Village, Taluka Mulshi, Pune – 411 042, State of Maharashtra, India
c) an Indian national.

a) **RAGHAVAN Vineeth**
b) Lupin Research Park, 46/47A, Nande Village, Taluka Mulshi, Pune – 411 042, State of Maharashtra, India
c) an Indian national.

a) **ARRA Ganga Srinivas**
b) Lupin Research Park, 46A/47A, Nande Village, Taluka Mulshi, Pune – 411 042, State of Maharashtra, India
c) an Indian national.

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application :

    a) Complete specification in quadruplicate.
    b) Statement and Undertaking on FORM -3 (in duplicate).
    c) Fee of Rs. 5000 in cheque No. 682889
       Date 26/04/2003 on Standard Chartered Bank.

We request that a patent may be granted to us for the said invention.

Dated this 26th day of April 2003.

ANJAN SEN
Of S. MAJUMDAR & CO.
Applicants' Agent

To
The Controller of Patents
The Patent Office
At Mumbai

FORM - 2

THE PATENTS ACT, 1970

(39 OF 1970)

COMPLETE SPECIFICATION

(See Section 10)

1. TITLE OF INVENTION

A CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION AND A PROCESS FOR PREPARING THE SAME

2. LUPIN LIMITED, of 159, CST Road, Kalina, Santacruz (East), Mumbai - 400 098, State of Maharashtra, India, an Indian Company.

OPEM
417/mum/2003
28.4.03

The following specification particularly describes the nature of the invention and the manner in which it is to be performed.

Complete specification treated as Provisional specification u/s 9(3) of the Patents Act, 1970 as amended by The Patents (Amendment) Act, 2002. Plain
(P.K.JAIN)
Examiner of Patents & Designs.

FIELD OF THE INVENTION

The present invention relates to antiretrovial pharmaceutical composition and in particular to an antiretrovial pharmaceutical composition having a selective combination of a controlled release active formulation and an immediate release active formulation for once daily administration.The invention also relates to the process for manufacture of such once daily antiretrovial pharmaceutical composition.

BACKGROUND OF THE INVENTION

Acquired Immune Deficiency Syndrome (AIDS) which is caused by the human immunodeficiency virus (HIV) is one of the few diseases for which mankind is struggling to find a cure.

In the last several years many anti-retroviral agents have been discovered that has since been used to treat AIDS. The drugs that are currently approved for anti-HIV therapy are broadly classified into three categories, namely:

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI), which include lamivudine, zidovudine, didanosine, abacavir, stavudine, and zalcitabine.
2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI), which include nevirapine, efavirenz, and delavirdine.
3. Protease Inhibitors (PI), which include indinavir, ritonavir, nelfinavir, saquinavir, and amprenavir.

For successful treatment of any disease caused by a micro-organism the drug used in the therapy should eliminate the causative organism completely without allowing them to undergo mutation. Mutation may lead to resistant strains which can make treatment more difficult. This development of resistant strains is usually observed when a single agent or drugs belonging to a single category are solely used in the treatment. For most diseases caused by micro-organisms, it has been found that combining two or more drugs, preferably from different classes have resulted in a greater success rate.

Drugs for the treatment of highly active anti-retroviral therapy were initially prescribed as a loose combination of two or three drugs. This was rationalised to fixed dose combinations to be administered twice daily. In our co-pending application number PCT/IN02/00110 we have described a formulation which further reduced the pill burden to once a day. However to date there are no reports of once a day formulation comprising a three drug combination.

There are three known alternative regimens as follows:

1) 3 NRTIs
2) 2 NRTIs + 1 NNRTI
3) 2 NRTIs + 1 PI

Nucleoside-based reverse transciptase inhibitors (NRTIs) were the first drugs to be given as antiretroviral agents, and they remain the backbone of therapy against HIV infection and acquired immuno deficiency syndrome (AIDS). Although various therapy regimens have been tried as indicated above, it has been reported that drug combination comprising three NRTIs is not as effective as other combinations. The combination of two NRTIs, lamivudine and zidovudine which form the backbone of therapy with one NNRTI such as Nevaripine is ideal. Nevaripine has a long half life of more than 25 hours and is currently given as 200 mg twice daily. We propose to use 400 mg Nevaripine to be given as a fixed dose combination with lamivudine and zidovudine once daily.

Multi-drug therapy in case of anti-retrovirals has the advantage that drugs have different mechanisms of action and act at different stages of the viral life cycle and they may exhibit a synergistic effect on such use. However, this kind of therapy results in the patient having to take multiple pills several times a day and this is known to cause problems of compliance in following the therapy regimen. Several attempts have been made to reduce the pill burden in order to enhance patient compliance.

Lamivudine 150mg and zidovudine 300mg are NRTIs that are to be given twice daily. A fixed dose combination of lamivudine 150mg and zidovudine 300mg

(COMBIVIR) has been developed which has reduced the pill load for this combination to two. Similarly, a three drug fixed dose combination of lamivudine 150 mg, zidovudine 300 mg and abacavir 300 mg (TRIZIVIR) has also been developed. However, there are reports of toxicity related to abacavir. Further, the frequency of dosing for both two and three drug combination is still twice daily.

United States Patent No. 6,113,920 discloses a pharmaceutical composition comprising two active pharmaceutical ingredients namely lamivudine and zidovudine and a pharmaceutically acceptable glidant ingrdient, selected from a group of colloidal silicon dioxide, microcrystalline cellulose, metallic stearates, calcium carbonate and combinations thereof, in the form of a film coated tablet. The composition contains lamivudine in an amount from 15 to 1500 mg per tablet and zidovudine in an amount from 30 to 1000 mg per tablet. This combination is given twice daily.

United States Patent No. 4,917,900 discloses a pharmaceutical formulation for oral administration in which discrete units comprising zidovudine are provided with a controlled release coating consisting of alkyl esters of acrylic and methacrylic acids and ethylcellulose in a weight ratio of 1:3 to 3:1. These spheroids contain atlease 80% of zidovudine and microcrystalline cellulose and mannitol as the core-forming agent.

As discussed above, while a two drug combination product may reduce the pill burden to half, it still has to be given twice daily and when coupled with a third drug, the pill burden is substantially increased.

OBJECTS OF THE INVENTION

It is thus the basic object of the present invention to provide for a three-drug antiretroviral pharmaceutical composition which would reduce the pill load and frequency of drug administration thereby favouring patient compliance and effective treatment.

Another object is to provide a fixed dose combination of lamivudine, zidovudine and nevirapine suitable for once daily administration which would reduce the pill burden to one and the frequency to once daily.

Yet further object of the present invention is directed to the development of a three drug fixed dose combination comprising essentially the antiretroviral drugs lamivudine, zidovudine, and nevirapine suitable for once daily dosing wherein lamivudine and zidovudine would have a controlled release while nevirapine will be immediately released.

Yet further object is directed to provide a process for preparing an antiretroviral pharmaceutical composition as above which would reduce the pill load and frequency of drug administration thereby favouring patient compliance and effective treatment.

SUMMARY OF THE INVENTION

Thus according to the present invention there is provided an antiretroviral pharmaceutical composition comprising a selective combination of

i. a controlled release formulation comprising :
   a. lamivudine or a pharmaceutically acceptable derivative thereof,
   b. zidovudine or a pharmaceutically acceptable derivative thereof, and
   c. a mixture of hydrophilic polymers, said polymers being selected from the group consisting of cellulose ethers, polyuronic acids and pharmaceutically acceptable gums or mixtures thereof and
   d. a pharmaceutically acceptable calcium salt.

ii. an immediate release formulation comprising atleast one selective Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI), preferably nevirapine or a pharmaceutically acceptable derivative thereof alongwith pharmaceutically acceptable excipients.

According to an aspect of the present invention there is provided an antiretroviral pharmaceutical composition in the form of a bilayer composition comprising a selective combination of

i. a first layer of said controlled release formulation comprising :

a. lamivudine or a pharmaceutically acceptable derivative thereof,
b. zidovudine or a pharmaceutically acceptable derivative thereof, and
c. a mixture of hydrophilic polymers, said polymers being selected from the group consisting of cellulose ethers, polyuronic acids and pharmaceutically acceptable gums or mixtures thereof and
d. a pharmaceutically acceptable calcium salt.

ii. a second layer of said immediate release formulation comprising atleast one selective Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI), preferably nevirapine or a pharmaceutically acceptable derivative thereof and pharmaceutically acceptable excipients.

According to another aspect of the present invention there is provided an antiretroviral pharmaceutical composition comprising a selective combination of

i. a core having a controlled release formulation comprising :

a. lamivudine or a pharmaceutically acceptable derivative thereof,
b. zidovudine or a pharmaceutically acceptable derivative thereof, and
c. a mixture of hydrophilic polymers, said polymers being selected from the group consisting of cellulose ethers, polyuronic acids and pharmaceutically acceptable gums or mixtures thereof and
d. a pharmaceutically acceptable calcium salt.

ii. an outer coat of an immediate release formulation comprising atleast one selective Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI), preferably nevirapine or a pharmaceutically acceptable derivative thereof and pharmaceutically acceptable excipients.

In accordance with yet another aspect of the invention there is provided a process for the preparation of a pharmaceutical composition comprising

(i) providing said controlled release formulation by mixing together active ingredients selected from amongst lamivudine, zidovudine or mixtures

thereof with hydrophilic polymers selected from amongst cellulose ethers, polyuronic acids, pharmaceutically acceptable gums or mixtures thereof, and with a pharmaceutically acceptable calcium salt, optionally a diluent and a lubricant,

(ii) providing said immediate release formulation nevirapine blended with pharmaceutically acceptable excipients and (iii) obtaining the composition of said controlled release formulation and immediate release formulation preferably by compressing the resulting blends into bilayered tablets.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with a preferred aspect in the above bilayered composition of the invention Lamivudine and Zidovudine are selectively provided as an extended release layer while the third drug nevirapine is provided as an immediate release layer.

The extended release layer is preferably obtained of said lamivudine and zidovudine alongwith a mixture of hydrophilic polymers selected from the group consisting of cellulose ethers, polyuronic acids, and pharmaceutically acceptable gums and a pharmaceutically acceptable calcium salt. The composition may also contain other pharmaceutically acceptable excipients both in the extended release layer as well as the second layer where nevirapine is present. The quantities of the essential and optional excipients are such that all three active ingredients are released at a rate suitable for once daily administration. The pharmaceutical composition is in the form of uncoated or coated bilayered tablet.

The effective therapeutic dose of the active ingredients that can be administered by compositions of the present invention include a combination 300 mg of lamivudine with 600 mg of zidovudine as well as 400 mg of nevirapine.

The pharmaceutical composition pertaining to this embodiment is preferably in the form of a bilayered tablet with the controlled release comprising one layer and the immediate release comprising the second layer. Alternatively the controlled release component may be in the form of a core and the second immediate release layer may be coated on top of the core.

The first layer of the pharmaceutical composition comprises lamivudine and zidovudine or their pharmaceutically acceptable derivatives along with a mixture of hydrophilic polymers selected from the group consisting of cellulose ethers, polyuronic acids, pharmaceutically acceptable gums, or mixtures thereof. In addition, this layer also comprises a pharmaceutically acceptable calcium salt and optionally one or more water soluble or water dispersible pharmaceutically acceptable excipients.

The cellulose ether used in accordance with the present invention is selected from amongst those commonly known in the art such as hydroxypropyl cellulose, hydoxypropyl methylcellulose, carboxy methylcellulose, sodium carboxymethylcellulose, ethyl cellulose, methyl cellulose, hydroxy ethylcellulose and the like. It is present in an amount from about 2% to about 12% by weight of the first layer.

The polyuronic acid used in accordance with the present invention is selected from amongst alginic acid, sodium alginate, calcium alginate, sodium calcium alginate, potassium alginate, ammonium alginate, magnesium alginate and the like. It is present in an amount from about 0.5% to about 10% by weight of the first layer.

The pharmaceutically acceptable gum is selected from amongst those commonly known in the art such as guar gum, xanthan gum, gum karaya, tragacanth gum, gum acacia and the like. It is present in an amount form about 0.1% to about 10% by weight of the first layer.

Calcium salts when used along with certain polymers, especially the alginates, have been known to stablise the matrix. In accordance with this, in a preferred embodiment, the said first layer of the composition also contains a pharmaceutically acceptable calcium salt.

The calcium salt is selected from the group consisting of calcium sulphate, calcium phosphate, calcium carbonate and calcium chloride. It is present in an amount from about 0.1% to about 2.5% by weight of the first layer.

The first layer of the composition may further contain one or more pharmaceutically acceptable other excipients selected from amongst water soluble and/or water dispersible diluents and lubricants.

The water dispersible or water soluble diluent selected from amongst microcrystalline cellulose, dicalcium phosphate, calcium carbonate, lactose, powdered cellulose, starch, mannitol and the like. It is present from about 1% to about 28% by weight of the first layer.

In another preferred embodiment, the diluent is microcrystalline cellulose and is present in an amount from about 5% to about 20% by weight of the first layer.

In another preferred embodiment, the diluent is dicalcium phosphate and is present in an amount from about 1% to about 5% by weight of the first layer.

The second layer of the composition of the present invention comprises nevirapine or its pharmaceutically acceptable derivative along with pharmaceutically acceptable excipients selected from the group consisting of diluents, binders, disintegrants, lubricants, coloring agents and the like.

The diluent is selected from amongst microcrystalline cellulose, dicalcium phosphate, calcium carbonate, lactose, powdered cellulose, starch, mannitol and the like. The diluent is present in an amount from about 2% to about 15% by weight of the second layer.

The second layer comprises atleast one binder selected from amongst carboxymethylcellulose sodium, povidone, pregelatinised starch, gelatin, and the like. The binder is present in an amount from about 1% to about 10% by weight of the second layer.

The disintegrant is selected from amongst crospovidone, sodium starch glycolate, pregelatinised starch, carboxymethylcellulose sodium, croscarmellose sodium, starch and the like. It is present in an amount from about 0.5% to about 15% by weight of the second layer.

According to the present invention each layer may also contain lubricants selected from amongst those commonly known in the art such as magnesium stearate, calcium stearate, stearic acid, silicon dioxide, talc and the like. It is present in an amount from about 0.1% to about 3% by weight.

The pharmaceutical compositions as described in this invention may be prepared by procedures well known to those skilled in the art. For the preparation of the granular blend for each layer, all the active ingredients along with the necessary excipients are mixed together and then compacted. The compacted mass is then comminuted to obtain the granules. Alternatively, the granules may also be prepared by the process of wet granulation using a suitable granulating agent.

In accordance with the requirements of the invention, the amount of fines incorporated in the blends of each layer before compression is in the range from 15% to 35% by weight. For the purpose of this invention, fines denote particles having size less than 250 microns.

The final granular blend of the two layers is compressed into bilayered tablets on a compression machine suitable for such purpose. The tablets may also be of the form wherein the controlled release layer is present as a core and the immediate release layer is present as a coat around the core. The tablets so obtained may be further coated using a water soluble polymer.

The above mentioned process results in a pharmaceutical composition that contains three anti retroviral agents in one tablet suitable for once daily administration. The effective therapeutic dose of the active that can be administered include a combination of 300 mg of lamivudine, 600 mg of zidovudine and 400 mg of nevirapine.

The objects of the invention and its advantages are explained hereunder in greater detail in relation to non-limiting examples hereunder :

Examples

Example 1

Ingredients	Weight (mg/tab)
FIRST LAYER	
Lamivudine	300
Zidovudine	600
Microcrystalline Cellulose	187
Hydroxypropyl methylcellulose	62.5
Sodium alginate	31.25
Guar gum	12.5
Calcium sulphate	3.75
Dicalcium phosphate	40
Magnesium Stearate	13
SECOND LAYER	
Nevirapine	400
Powdered Cellulose	52.5
Povidone K30	20
Sodium starch glycolate	15
Magnesium stearate	3.75
Sodium starch glyclote	5
Colloidal silicon dioxide	2.5
Magnesium stearate	1.25

First Layer blend: Lamivudine, zidovudine , hydrophilic polymers, calcium sulphate, dicalcium phosphate, and microcrystalline cellulose were screened through 30 no. mesh and mixed with magnesium stearate. The blend was compacted and the slugs obtained were milled to form granules. The sized granules were blended with fines and lubricated.

Second Layer blend: Nevirapine, cellulose, povidone and a first portion of sodium starch glycollate were screened through 40 no. mesh and mixed with magnesium stearate. The blend was compacted and the slugs obtained were

milled to form granules. The granules were mixed with a second portion of sodium starch glycollate, colloidal silicon dioxide and lubricated.

Bilayered tablets: Both the above blends were compressed into bilayered tablets using a bilayered tablet compression machine.

Drug Release: The tablets were tested for release of all three actives using USP Type 1 Dissolution apparatus at an RPM of 100 and with 900ml of 0.1N HCL for the first 2 hrs and pH 6.8 Phosphate buffer afterwards. The release obtained is as follows:

Time	% Drug released		
	Lamivudine	Zidovudine	Nevirapine
1hr	29.1	17.1	87.1
2hrs	42.7	25.9	
4hrs	55.5	42.3	
8hrs	70.4	67.6	
10hrs	79.4	80.1	
12hrs	85.3	88.2	

Example 2

Ingredients	Weight (mg/tab)
FIRST LAYER	
Lamivudine	300
Zidovudine	600
Microcrystalline Cellulose	187
Hydroxypropyl methylcellulose	62.5
Sodium alginate	31.25
Guar gum	12.5
Calcium sulphate	3.75
Dicalcium phosphate	40
Magnesium Stearate	13
SECOND LAYER	
Nevirapine	400
Powdered Cellulose	42.5
Povidone K30	10
Crospovidone	20

Sodium starch glycolate	15
Magnesium stearate	3.75
Sodium starch glyclote	5
Colloidal silicon dioxide	2.5
Magnesium stearate	1.25

The manufacturing procedure followed is substantially the same as shown in Example 1

The release obtained of the drugs is as follows:

Time	% Drug released		
	Lamivudine	Zidovudine	Nevirapine
1hr	33.8	21.3	97.1
2hrs	50.5	31	
4hrs	67.8	49.5	
8hrs	79.2	74	
10hrs	86.2	83.7	
12hrs	90.6	90.1	

Example 3

Ingredients	Weight (mg/tab)
Core	
Lamivudine	300
Zidovudine	600
Microcrystalline Cellulose	187
Hydroxypropyl methylcellulose	62.5
Sodium alginate	31.25
Guar gum	12.5
Calcium sulphate	3.75
Dicalcium phosphate	40
Magnesium Stearate	13
Coat	
Nevirapine	400
Powdered Cellulose	32.5
Povidone K30	20
Crospovidone	20
Sodium starch glycolate	15
Magnesium stearate	3.75

Sodium starch glyclote	5
Colloidal silicon dioxide	2.5
Magnesium stearate	1.25
Sunset Yellow FCF	2.5

Core :Lamivudine, zidovudine , hydrophilic polymers, calcium sulphate, dicalcium phosphate, and microcrystalline cellulose were screened through 30 no. mesh and mixed with magnesium stearate. The blend was compacted and the slugs obtained were milled to form granules. The sized granules were blended with fines, lubricated and compressed into a tablet.

Coat: Nevirapine, cellulose, povidone and a first portion of sodium starch glycollate were screened through 40 no. mesh and mixed with magnesium stearate. The blend was compacted and the slugs obtained were milled to form granules. The granules were mixed with a second portion of sodium starch glycollate, colloidal silicon dioxide,lubricated and compression coated over the core tablet.

The release obtained of the drugs is as follows:

Time	% Drug released		
	Lamivudine	Zidovudine	Nevirapine
1hr	37.4	22.8	80.8
2hrs	54.1	32.1	
4hrs	66.5	47.5	
8hrs	82.5	76.8	
10hrs	92	87.3	
12hrs	97.3	93.7	

It is thus apparent from the above exemplary illustrations that the pharmaceutical composition of the invention serves as an effective three-drug antiretroviral combination for once daily dosage for an effective combination treatment especially of NRTIs and NNRTIs. The once daily dosage form of the invention is simple and cost-effective and would serve in reducing the pill burden and frequency of administration and favour patient compliance with the desired drug regime for effective treatment.

WE CLAIM

1. An antiretroviral pharmaceutical composition comprising a selective combination of

   i. a controlled release formulation comprising :

      a. lamivudine or a pharmaceutically acceptable derivative thereof,
      b. zidovudine or a pharmaceutically acceptable derivative thereof, and
      c. a mixture of hydrophilic polymers, said polymers being selected from the group consisting of cellulose ethers, polyuronic acids and pharmaceutically acceptable gums or mixtures thereof and
      d. a pharmaceutically acceptable calcium salt.

   ii. an immediate release formulation comprising atleast one selective Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI), preferably nevirapine or a pharmaceutically acceptable derivative thereof alongwith pharmaceutically acceptable excipients.

2. An antiretroviral pharmaceutical composition as claimed in claim 1 in the form of a bilayer composition comprising a selective combination of

   i. a first layer of said controlled release formulation comprising :

      a. lamivudine or a pharmaceutically acceptable derivative thereof,
      b. zidovudine or a pharmaceutically acceptable derivative thereof, and
      c. a mixture of hydrophilic polymers, said polymers being selected from the group consisting of cellulose ethers, polyuronic acids and pharmaceutically acceptable gums or mixtures thereof and
      d. a pharmaceutically acceptable calcium salt.

   ii. a second layer of said immediate release formulation comprising atleast one selective Non-nucleoside Reverse Transcriptase Inhibitor

(NNRTI), preferably nevirapine or a pharmaceutically acceptable derivative thereof and pharmaceutically acceptable excipients.

3. An antiretroviral pharmaceutical composition as claimed in claim 1 comprising a selective combination of

i. a core having a controlled release formulation comprising :

a. lamivudine or a pharmaceutically acceptable derivative thereof,
b. zidovudine or a pharmaceutically acceptable derivative thereof, and
c. a mixture of hydrophilic polymers, said polymers being selected from the group consisting of cellulose ethers, polyuronic acids and pharmaceutically acceptable gums or mixtures thereof and
d. a pharmaceutically acceptable calcium salt.

ii. an outer coat of an immediate release formulation comprising atleast one selective Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI), preferably nevirapine or a pharmaceutically acceptable derivative thereof and pharmaceutically acceptable excipients.

4. The composition as claimed in anyone of claims 1 to 3 wherein the amount of lamivudine or pharmaceutically acceptable derivative thereof is from about 50 mg to about 500 mg .

5. The composition as claimed in claim 4 wherein the amount of lamivudine or pharmaceutically acceptable derivative thereof is 300 mg .

6. The composition as claimed in anyone of claims 1 to 3 wherein the amount of zidovudine or pharmaceutically acceptable derivative thereof is from about 100 mg to about 1000 mg.

7. The composition as claimed in claim 6, wherein the amount of zidovudine or pharmaceutically acceptable derivative thereof is 600 mg .

8. The composition as claimed in anyone of claims 1 to 3 wherein the amount of nevirapine or pharmaceutically acceptable derivative thereof is from about 75 mg to about 750 mg.

9. The composition as claimed in claim 8 wherein the amount of nevirapine or pharmaceutically acceptable derivative thereof is 400 mg .

10. A composition as claimed in anyone of claims 1 to 3 wherein the cellulose ether is selected from amongst hydroxypropyl cellulose, hydoxypropyl methylcellulose, carboxy methylcellulose, sodium carboxymethylcellulose, ethyl cellulose, methyl cellulose, hydroxy ethylcellulose and the like.

11. A composition as claimed in claim 10 wherein the cellulose ether is hydroxypropyl methyl cellulose and is present in an amount from about 2% to about 12% by weight of the controlled release formulation.

12. A composition as claimed in anyone of claims 1 to 3 wherein the polyuronic acid is selected from amongst alginic acid, sodium alginate, calcium alginate, sodium calcium alginate, potassium alginate, ammonium alginate, magnesium alginate and the like.

13. A composition as claimed in claim 12 wherein the polyuronic acid is sodium alginate and is present in an amount from about 0.5% to about 10% by weight of the controlled release formulation.

14. A composition as claimed in anyone of claims 1 to 3 wherein the pharmaceutically acceptable gum is selected from amongst guar gum, xanthan gum, gum karaya, tragacanth gum, gum acacia and the like.

15. A composition as claimed in claim 14 wherein the pharmaceutically acceptable gum is guar gum and is present in an amount form about 0.1% to about 10% by weight of the controlled release formulation.

16. The composition as claimed in anyone of claims 1 to 3 wherein the pharmaceutically acceptable calcium salt is selected from the group consisting of calcium sulphate, calcium phosphate, calcium carbonate and calcium chloride.

17. A composition as claimed in claim 16 wherein the pharmaceutically acceptable calcium salt is calcium sulphate and is present in an amount from about 0.1% to about 2.5% by weight of the controlled release formulation.

18. The composition as claimed in anyone of claims 1 to 3 wherein the controlled release formulation further comprises at least one water dispersible or water soluble diluent selected from amongst microcrystalline cellulose, dicalcium phosphate, calcium carbonate, lactose, powdered cellulose, starch, mannitol and the like.

19. The composition as claimed in claim 18 wherein the diluent is present from about 1% to about 28% by weight of the controlled release formulation.

20. The composition as claimed in claim 19 wherein the diluent is microcrystalline cellulose.

21. The composition as claimed in claim 20 wherein the amount of microcrystalline cellulose is from about 5% to about 20% by weight.

22. The composition as claimed in claim 19 wherein the diluent is dicalcium phosphate.

23. The composition as claimed in claim 22 wherein the amount of dicalcium phosphate is from about 1% to about 5% by weight.

24. The composition as claimed in anyone of claims 1 to 3 wherein the controlled release formulation further comprises at least one lubricant

selected from amongst magnesium stearate, calcium stearate, stearic acid, silicon dioxide, talc and the like.

25. The composition as claimed in claim 24 wherein the lubricant is present from about 0.1% -3% by weight.

26. The composition as claimed in anyone of claims 1 to 3 wherein the immediate release formulation comprises from about 10% to about 95% by weight of nevirapine or a pharmaceutically acceptable derivative thereof along with one or more pharmaceutically acceptable excipients selected from amongst diluents, binders, disintegrants, lubricants, coloring agents and the like.

27. A composition as claimed in claim 26 wherein the diluent is selected from amongst microcrystalline cellulose, dicalcium phosphate, calcium carbonate, lactose, powdered cellulose, starch, mannitol and the like.

28. A composition as claimed in claim 27 wherein the diluent is powdered cellulose and is present in an amount from about 2% to about 15% by weight of the immediate release formulation.

29. A composition as claimed in claim 26 wherein the binder is selected from amongst carboxymethylcellulose sodium, povidone, pregelatinised starch, gelatin or mixtures therof.

30. A composition as claimed in claim 29 wherein the binder is present in an amount from about 1% to about 10% by weight of the immediate release formulation.

31. A composition as claimed in claim 26 wherein the disintegrant is selected from amongst crospovidone, sodium starch glycolate, pregelatinised starch, carboxymethylcellulose sodium, croscarmellose sodium, starch and mixtures thereof.

32. A composition as claimed in claim 31 wherein the disintegrant is present in an amount from about 0.5% to about 15% by weight of the immediate release formulation.

33. The composition as claimed in claim 26 wherein the lubricant is selected from amongst magnesium stearate, calcium stearate, stearic acid, silicon dioxide, talc and the like.

34. The composition as claimed in claim 33 wherein the lubricant is present from about 0.1% -3% by weight.

35. The composition as claimed in claim 1 in the form of a bilayered tablet of said controlled release formulation and said immediate release formulation.

36. The composition as claimed in claim 1, wherein said controlled release formulation is in the form of a core and said immediate release formulation is coated on said core.

37. A process for the preparation of a pharmaceutical composition comprising (i) providing said controlled release formulation by mixing together active ingredients selected from amongst lamivudine, zidovudine or mixtures thereof with hydrophilic polymers selected from amongst cellulose ethers, polyuronic acids, pharmaceutically acceptable gums or mixtures thereof, and with a pharmaceutically acceptable calcium salt, optionally a diluent and a lubricant, (ii) providing said immediate release formulation by blending nevirapine with pharmaceutically acceptable excipients and (iii) obtaining the composition therefrom preferably by compressing the resulting blends into bilayered tablets.

38. A process as described in claim 37 wherein each blend for the said controlled release and immediate release formulations may be dry granulated prior to compression.

39. A process as described in claim 37 wherein each blend for the said controlled release and immediate release formulations may be wet granulated prior to compression.

40. An antiretroviral pharmaceutical composition and a process for preparing the same substantially such as herein described and illustrated with reference to the accompanying examples.

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